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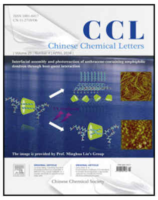

Original article

La_2O_3/TFE: An efficient system for room temperature synthesis of Hantzsch polyhydroquinolines

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ABSTRACT

Lanthanum oxide (La_2O_3) in combination with 2,2,2-trifluoroethanol (TFE) was found to be an efficient system for the one-pot, four-component synthesis of Hantzsch polyhydroquinoline derivatives from aromatic aldehydes, dimedone, ethyl acetoacetate and ammonium acetate at ambient temperature. The catalyst is heterogeneous and reusable, hence can be separated easily and reused. The present method is featured by mild reaction conditions, use of heterogeneous catalyst, non-chromatographic purification, short reaction time and high yields, which make it an attractive route for the synthesis of polyhydroquinolines.

1. Introduction

During the past decade, multi-component reactions (MCRs) have become an area of prime interest in synthetic organic chemistry due to their ability in converting more than two components in a single step to complex molecules. MCRs have emerged as efficient, atom economic, time saving and powerful tools in modern synthetic organic chemistry for the synthesis of pharmacologically and biologically important targets as they increase the efficiency of the reaction and avoid the multiple steps along with saving solvents and chemicals. Such reactions allow the formation of new bonds resulting in diverse molecular complexity in a single step [1]. MCRs play a prominent role in modern drug discovery processes [2]. Thus the study of MCRs has become one of the most attractive synthetic strategies preferred by organic chemists in industry and academia.

Derivatives of 1,4-dihydropyridine and polyhydroquinoline heterocyclic scaffolds are important classes of well known Ca^{2+} channel blockers and constitute the skeletons of drugs used in the treatment of hypertension and cardiovascular diseases [3]. These compounds possess a variety of biological activities including antidiabetic, antitumor, vasodilator, bronchodilator, geroprotective and anti-atherosclerotic properties [4]. They are also explored as antiischemics and in the treatment of Alzheimer's disease [5]. These facts reflect the remarkable pharmacological and medicinal potential of 1,4-dihydropyridines and polyhydroquinolines as drug candidates of therapeutic significance and as intermediates in organic synthesis. Thus the synthesis of these heterocyclics has become an area of great interest.

Traditionally 1,4-dihydropyridine and polyhydroquinolines are synthesized by refluxing aldehydes with 1,3-dicarbonyl compound and ammonium acetate catalyzed by acidic or basic catalysts. Literature survey reveals the availability of numerous methods for the synthesis of polyhydroquinoline derivatives using catalysts such as $HClO_4$–SiO_2 [6], ZnO [7], CuO [8], nano-Ni [9], *t*-BuOK [10], $Yb(OTf)_3$ [11], $Sc(OTf)_3$ [12], GuHCl [13], TiO_2 [14], scolecite [15], morpholine [16], Zn-VCO_3 hydrotalcite [17], magnetic Fe_3O_4 nanoparticles [18], Mn(III) complex [19], *etc.* The synthesis in aqueous medium [20] without catalyst although successful, requires longer reaction time (2.25–8 h). Thus many of the existing strategies suffer from harsh reaction conditions, use of stoichiometric and/or relatively expensive reagents, long reaction time, unsatisfactory yield of products, *etc.* Some of these methods, for example microwave or ultrasound assisted synthesis [21], require additional equipment such as a microwave oven or a soniccation bath. Ionic liquids [22] have also been used for clean chemical reactions replacing volatile organic solvents. But they suffer from inherent problems in separation and tedious workup is often involved. Consequently, research continues in the development of novel and facile protocols for the synthesis of polyhydroquinolines with improved operational simplicity, economic viability, reusability and milder reaction conditions.

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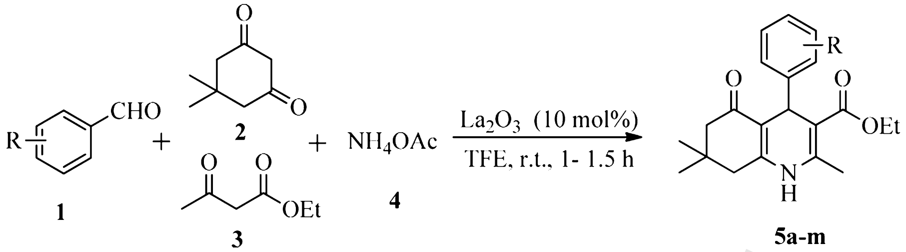

Scheme 1. Synthesis of Hantzsch polyhydroquinoline derivatives by using La_2O_3/TFE.

Recently, the characteristic features of fluorinated solvents such as high polarity, strong hydrogen accepting ability and low boiling points prompted their applications in organic synthesis. 2,2,2-Trifluoroethanol (TFE) is a low boiling (bp 74 °C), colorless and water miscible organic solvent. It has become one of the more widely used fluorinated solvents. It exhibits stronger acidic character and higher stability than the non-fluorinated alcohol due to the presence of the electronegative trifluoromethyl group. TFE is commonly used as a fluorinated alcohol on commercial scale manufacture processes. TFE has been used as an alternative to metal-assisted syntheses including several multi-component reactions such as the synthesis of dibenzo[c,e]azepinones, 1,3,4-trisubsituted pyrazoles, reductive alkylation, *etc.* [23].

Several inorganic metal oxides, such as ZnO, CuO, Al_2O_3, TiO_2, *etc.* act as efficient heterogeneous catalysts due to their Lewis acid–base characters and ability to provide large surface area for adsorption of organic molecules [24]. Lanthanum oxide (La_2O_3), also known as *Lanthana*, is a white, odorless, and large band gap (5.5 eV) rare earth metal oxide with a high dielectric constant ($\varepsilon = 27$). It is thermally stable (melting point 2315 °C), cheap, readily available and insoluble in water. Consequently it can be employed in organic synthesis as an effective heterogeneous catalyst. In recent years, lanthanum oxide and its composites came into limelight as catalysts in organic synthesis such as carbonylation of glycerol [25], C–N coupling reactions [26], Heck reaction [27], Wittig reaction [28], *etc.* In continuation of our efforts in the development of new synthetic routes for the synthesis of heterocyclic compounds using reusable heterogeneous catalysts [29], we report the combination of TFE/La_2O_3 as an efficient tool for the one-pot, four-component synthesis of polyhydroquinolines at room temperature in excellent yields (Scheme 1).

2. Experimental

All the chemicals were purchased from SD fine chemicals Ltd and used without further purification. The synthesized polyhydroquinoline derivatives were confirmed on the basis of spectral data and comparison of their physical constants to those reported in literature. Melting points were measured in capillaries open at one end and were uncorrected. The progress of reaction was monitored by thin-layer chromatography (TLC) analysis in 30% EA: Hexane. ^1H NMR spectra were recorded in $CDCl_3$ on a 400 MHz Varian spectrophotometer using tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded on a Shimadzu FTIR spectrometer using KBr pellets. Samples were analyzed for exact mass on a Shimadzu mass analyzer.

General procedure for the synthesis of Hantzsch polyhydroquinoline derivatives: in a typical condensation reaction, a mixture of aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1.2 mmol), ammonium acetate (1.5 mmol) and La_2O_3 (10 mol%) in TFE (2 mL) was magnetically stirred at room temperature for appropriate time as specified in Table 1. After the completion of the reaction as monitored by TLC (30% EA: Hex) analysis, the reaction mixture was diluted with hot TFE, and the catalyst was filtered off. The filtrate was concentrated and the crude was purified by recrystallization from ethanol to afford the pure polyhydroquinoline derivatives.

The structures of the synthesized products were confirmed by comparison of their melting points with authentic values reported in literature and spectral techniques-^1H NMR, IR, elemental analysis and ESMS. The spectral data of representative compounds are described below:

Ethyl-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenyl-quinoline-3-carboxylate (**5a**): Faint yellow solid, Mp. 202–204 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 3H, CH_3), 1.1 (s, 3H, CH_3), 1.2 (t, 3H, CH_3), 2.15–2.35 (m, 4H), 2.4 (s, 3H), 4.05 (q, 2H), 5.03 (s, 1H), 6.02 (brs, 1H, NH), 7.1–7.4 (m, 5H). IR (KBr, cm^{-1}): ν 3285.88, 3082.38, 2954.11, 1697.43, 1609.67. Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.31, H, 7.42, N, 4.13. Found: C, 72.43, H, 7.029, N, 3.97.

Table 1
TFE mediated La_2O_3 catalyzed synthesis of polyhydroquinoline derivatives.

Entry	R	Product	Time (min)	Yield (%)[a]	Mp. (°C) [Ref.]
1	H	**5a**	60	90	202–204 [6]
2	4-Cl	**5b**	60	95	244–246 [6]
3	4-OMe	**5c**	70	88	259–261 [20]
4	3,4-Methylene dioxy	**5d**	65	92	209–211 [20]
5	4-SMe	**5e**	70	94	240–242 [8]
6	4-Me	**5f**	70	86	260–262 [16]
7	4-NO_2	**5g**	85	87	241–243 [6]
8	4-OH	**5h**	90	89	230–232 [9]
9	4-OH-3-OMe	**5i**	90	91	208–210 [9]
10	3,4(OMe)$_2$	**5j**	90	86	287–289 [20]
11	2-Furyl	**5k**	80	89	246–248 [6]
12	4-F	**5l**	70	88	183–185 [8]
13	4-NMe_2	**5m**	90	87	261–263 [6]

[a] *Reactions conditions*: aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1.2 mmol) and ammonium acetate (1.5 mmol), La_2O_3 (10 mol %) in TFE (2 mL), room temperature.

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Ethyl-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**5b**): Yellow solid, Mp 244–246 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.07 (s, 3H), 1.2 (t, 3H), 2.15–2.30 (m, 4H), 2.4 (s, 3H), 4.04 (q, 2H), 5.03 (s, 1H), 5.82 (brs, 1H, NH), 7.15–7.20 (d, 2H, J = 8.4 Hz), 7.20–7.30 (d, 2H, J = 8.4 Hz) IR (KBr, cm^{-1}): ν 3274.31, 3077.56, 2958.93, 1705.15, 1647.28, 1602.91. Anal. Calcd. for $C_{21}H_{24}ClNO_3$: C, 67.46, H, 6.47, N, 3.75. Found: C, 67.55, H, 6.38, N, 3.68, ES-MS: 396.03 [M+Na]$^+$.

Ethyl-4-(benzo[d][1,3]dioxol-6-yl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**5d**): Faint yellow solid, Mp 209–211 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.23 (t, 3H), 2.13–2.35 (m, 4H), 2.35 (s, 3H), 4.07 (q, 2H), 4.98 (s, 1H), 5.87 (s, 2H), 6.08 (brs, 1H, NH), 6.6–6.83 (m, 3H), IR (KBr, cm^{-1}): ν 3273.34, 3077.56, 3198.11, 1696.47, 1604.84, 1031.00, 884. Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.91, H, 6.57, N, 3.65. Found: C, 66.54, H, 6.415, N, 3.34, ES-MS: 406.04 [M+Na]$^+$.

Ethyl-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-4-(4-(methylthio)phenyl)-5-oxoquinoline-3-carboxylate (**5e**): Yellow solid, Mp 240–242 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 3H, CH_3), 1.1 (s, 3H, CH_3), 1.21 (t, 3H), 2.1–2.3 (m, 4H), 2.38 (s, 3H), 2.42 (s, 3H), 4.07 (q, 2H), 5.0 (s, 1H), 6.02 (brs, 1H, NH), 7.05–7.20 (d, 2H, J = 7.2 Hz), 7.20–7.35 (d, 2H, J = 7.2 Hz) IR (KBr, cm^{-1}): ν 3277.20, 3077.56, 2958.93, 1700.32, 1601.95, 1487.18, 1367.59, 1279.82, 1231. Anal. Calcd. for $C_{22}H_{27}NO_3S$: C, 68.54, H, 7.06, N, 3.63. Found: C, 68.47, H, 6.917, N, 3.53, ES-MS: 408.02 [M+Na]$^+$.

3. Results and discussion

The acidic nature of fluorinated organic solvents primarily arises from the fluorine atoms. The presence of an electronegative trifluoromethyl group in TFE affords it strong acidic character. Lanthanum oxide has temperature dependent crystal structure [30]. At ambient temperature, it has a hexagonal crystal structure in which the La^{3+} ion (Lewis acid) is surrounded by 7 co-ordinate group of O^{2-} ions (Fig. 1).

At higher temperature, it becomes a cubic crystal. These basic structural features prompted us to use the combination of these two in organic synthesis for the construction of heterocyclic compounds such as Hantzsch polyhydroquinoline derivatives. To optimize the reaction conditions and select proper solvent, the reaction of 4-Cl-benzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1.2 mmol) and ammonium acetate (1.5 mmol) using La_2O_3 (10 mol%) catalyst in 2 mL of respective solvent was chosen as the model condensation reaction whose results are summarized in Table 2.

Initially the reaction was tried at room temperature in the absence of any catalyst and solvent. When the reaction was carried at room temperature in the absence of catalyst, it could not complete even after a long time (24 h) (Table 2, entry 1). Then we continued to optimize the model condensation using various solvents and their combinations. The use of solvents such as DMSO or DMF at ambient temperature resulted in low yield of the corresponding polyhydroquinolines after 3–4 h. Binary solvent systems such as EtOH:H_2O (1:1) or THF:H_2O (1:1) could not improve the results. Acetonitrile could accomplish moderate yield (56%). From the literature survey, ethanol is a common solvent employed for the synthesis of 1,4-dihydropyridine and polyhydroquinolines. When the reaction was carried in ethanol, the yield was improved and the reaction time was shortened to some extent. However, excellent yields with short reaction time were possible with the use of 2,2,2-trifluoroethanol (TFE). To study the temperature effect in the TFE-mediated synthesis of polyhydroquinolines, a reaction was carried in the absence of catalyst by simply refluxing a mixture of 4-chlorobenzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate in which a good yield of the corresponding polyhydroquinoline (89%) was obtained but the reaction required 5 h for completion. Furthermore, to determine the amount of the catalyst in this reaction, the reactions were carried with different concentrations of La_2O_3. The rise in catalyst concentration from 10 to 15 or 20 mol% could neither enhance the yield of product nor reduce the time to below 1 h. Thus, excellent results were obtained with 10 mol% of La_2O_3 in TFE at room temperature in terms of yield as well as time. The scope and generality of the one-pot, four-component synthesis of polyhydroquinoline derivatives through the Hantzsch reaction was verified with different aldehydes under these optimized conditions. Almost all aldehydes, possessing both electron-donating as well as electron withdrawing groups along with heterocyclic aldehydes reacted smoothly with clean reaction profile to afford the corresponding polyhydroquinoline derivatives.

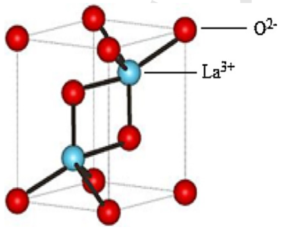

Fig. 1. Structure of La_2O_3.

Table 2
Solvent screening for La_2O_3 catalyzed synthesis of polyhydroquinolines.

Entry	Solvent	Time (h)	Yield (%)[a]
1	No catalyst, no solvent	24	27
2	DMSO	3	26
3	DMF	4	17
4	EtOH	2.5	67
5	50% EtOH:H_2O	2.5	58
6	THF:H_2O (1:1)	2.5	53
7	H_2O	3.5	32
8	ACN	2	56
9	TFE	1	89[b], 95

[a] Isolated yield.
[b] Reaction carried in the absence of catalyst under reflux in TFE for 5 h.

No significant substituent effect was observed in terms of reaction time and yield of the product. Furthermore, reusability study of the catalyst showed good results. 4-Chlorobenzaldehyde gave 95%, 91%, 88%, 85% yield of the ethyl 4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate after fresh, 1st, 2nd and 3rd run, respectively. The catalyst can be recycled and reused several times without much loss of catalytic activity (Table 3).

Thus, the present protocol tolerates different functional groups, such as methoxy, hydroxyl, halide, *etc.*, and smoothly affords the polyhydroquinolines in short reaction time at room temperature in excellent yields. A comparative study of the effect of La_2O_3/TFE combination with some of the literature methods for the synthesis of polyhydroquinolines is summarized in Table 4.

Table 3
Reusability of La_2O_3 catalyst.

Run	Fresh	I	II	III
Yield (%)[a]	95	91	88	85

[a] Yields in case of 4-chlorobenzaldehyde.

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Table 4
Comparison of La_2O_3/TFE combination with literature methods for the synthesis of polyhydroquinolines.

Entry	Catalyst	Conditions	Yield (%)	Reference
1	$HClO_4$–SiO_2 (50 mg/mmol)	90 °C, neat, 8–20 min	81–96	[6]
2	ZnO (10 mol%)	80 °C, 1 h	81–94	[7]
3	$Yb(OTf)_3$ (5 mol%)	EtOH, r.t., 2–8 h	85–95	[11]
4	$Sc(OTf)_3$ (5 mol%)	EtOH, r.t., 2–6 h	85–95	[12]
5	Scolecite (100 mg/mmol)	EtOH, reflux, 35–60 min	81–95	[15]
6	No catalyst	H_2O, reflux, 2.25–8 h	90–99	[20]
7	La_2O_3 (10 mol%)	TFE, r.t., 1–1.5 h	86–95	Present work

4. Conclusion

Thus in the present work, we have demonstrated the utility of the combination of lanthanum oxide and trifluoroethanol (La_2O_3/TFE) for the synthesis of Hantzsch polyhydroquinolines from aromatic aldehydes, dimedone, ethylacetoacetate and ammonium acetate at room temperature. The presence of Lewis acidic sites (La^{3+}) in the catalyst and trifluoromethyl group in TFE increased Lewis acidity of the combination of La_2O_3/TFE system, which was sufficient enough to catalyze the reaction at ambient temperature affording high yield of products in short reaction time. Use of heterogeneous catalyst, tolerance to various substituents, easy separation, short reaction time and high yield are the significant advantages associated with the present protocol, which make it an attractive strategy for the synthesis of polyhydroquinolines. Thus, the present protocol highlights and explores not only the applications of 2,2,2-trifluoroethanol as a powerful solvent in organic synthesis but also the emerging utility of La_2O_3 as a heterogeneous catalyst for the synthesis of heterocyclic compounds. We strongly believe that the combination will find extensive applications in future for the synthesis of heterocyclic compounds.

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